PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61L 15/00, A61K 9/70, 35/14, 38/00, A01N 1/02

A1

(11) International Publication Number: WO 97/28832

(43) International Publication Date: 14 August 1997 (14.08.97)

(21) International Application Number: PCT/US97/01901

(22) International Filing Date: 6 February 1997 (06.02.97)

(30) Priority Data:
60/011,216 6 February 1996 (06.02.96) US

(71) Applicant *(for all designated States except US)*: NEW GENERATION MEDICAL CORPORATION [US/US]; 3960 Vanessa Drive, Las Vegas, NV 89103 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: KOSOW, David, P. [US/US]; 6 Sylvan Glen, Phoenixville, PA 19460 (US).

(74) Agent: NOONAN, William, D.; Klarquist, Sparkman, Campbell, Leigh & Whinston, L.L.P., One World Trade Center, Suite 1600, 121 S.W. Salmon Street, Portland, OR 97204 (US).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: COMPOSITION FOR SEALING WOUNDS

(57) Abstract

A hemostatic bandage contains powdered fibrinogen and thrombin adhered to a fibrous matrix with a viscous, nonaqueous adhesive such as a viscous polysaccharide, glycol, or petroleum jelly. The nonaqueous adhesive does not allow a hydrolytic reaction to occur between the fibrinogen and thrombin until the bandage is moistened by a body fluid, such as blood. Hence the bandage can be prepared and stored for prolonged periods while retaining hemostatic activity.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	**GB**	United Kingdom	**MW**	Malawi
AT	Austria	**GE**	Georgia	**MX**	Mexico
AU	Australia	**GN**	Guinea	**NE**	Niger
BB	Barbados	**GR**	Greece	**NL**	Netherlands
BE	Belgium	**HU**	Hungary	**NO**	Norway
BF	Burkina Faso	**IE**	Ireland	**NZ**	New Zealand
BG	Bulgaria	**IT**	Italy	**PL**	Poland
BJ	Benin	**JP**	Japan	**PT**	Portugal
BR	Brazil	**KE**	Kenya	**RO**	Romania
BY	Belarus	**KG**	Kyrgystan	**RU**	Russian Federation
CA	Canada	**KP**	Democratic People's Republic of Korea	**SD**	Sudan
CF	Central African Republic			**SE**	Sweden
CG	Congo	**KR**	Republic of Korea	**SG**	Singapore
CH	Switzerland	**KZ**	Kazakhstan	**SI**	Slovenia
CI	Côte d'Ivoire	**LI**	Liechtenstein	**SK**	Slovakia
CM	Cameroon	**LK**	Sri Lanka	**SN**	Senegal
CN	China	**LR**	Liberia	**SZ**	Swaziland
CS	Czechoslovakia	**LT**	Lithuania	**TD**	Chad
CZ	Czech Republic	**LU**	Luxembourg	**TG**	Togo
DE	Germany	**LV**	Latvia	**TJ**	Tajikistan
DK	Denmark	**MC**	Monaco	**TT**	Trinidad and Tobago
EE	Estonia	**MD**	Republic of Moldova	**UA**	Ukraine
ES	Spain	**MG**	Madagascar	**UG**	Uganda
FI	Finland	**ML**	Mali	**US**	United States of America
FR	France	**MN**	Mongolia	**UZ**	Uzbekistan
GA	Gabon	**MR**	Mauritania	**VN**	Viet Nam

COMPOSITION FOR SEALING WOUNDS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to a composition of and method for producing a hemostatic dressing consisting of a carrier, a binding agent and substances of animal or human origin that are conducive to the coagulation of blood and/or the healing of wounds, and is capable of stopping bleeding, especially arterial bleeding.

Background of the Invention

It has been known to use various types of materials containing blood clotting substances to close and cover wounds. A difficulty in producing these materials is the necessity of preventing the coagulation substances, notably fibrinogen and thrombin, from reacting prior to use. One approach to preventing the clotting factors from reacting with each other prior to use has been to provide a layered collagen sheet containing fibrinogen on one layer and thrombin on an adjacent layer as described in U.S. Patents 4,606,337 and 4,683,142. A disadvantage of this method is that the fibrinogen and thrombin are not in close contact with each other and must mix after being applied to the wound. This could cause a delay in the onset of coagulation. Another disadvantage of this method is the necessity of having to manufacture several different layers and then assemble them in the proper order. Furthermore, this patent describes the use of only glycoproteins as the carrier matrix and is not applicable to other materials.

A tissue adhesive is disclosed in U.S. Patent 4,600,574 which uses a tissue compatible material selected from the group consisting of collagen, gelatin and polysaccharide. This material is impregnated with fibrinogen and Factor XIII and then lyophilized This material does not contain thrombin, and relies on endogenous thrombin production at the wound site. This is an obvious disadvantage especially where there is consumptive coagulopathy or any other reason for insufficient thrombin to be produced to rapidly form a clot with the fibrinogen supplied on the material being applied to the wound.

U.S. Patent 4,442,655 discloses the preparation, manufacture and use of a preparation in which the fibrinogen and thrombin are allowed to react to

form the material which is then used as a wound toilet material, a filling material for bone cavities and/or as a support material for other substances. This is not a hemostatic product.

A composition for sealing and healing wounds is disclosed in U.S. Patent 4,453,939. This composition is a collagen matrix to which fibrinogen and thrombin are added in the presence of an organic solvent such as alcohols, ketones, ethers, esters, and halogenated hydrocarbons. These organic solvents are known to inactivate and denature proteins such as fibrinogen and thrombin with denaturation occurring more rapidly as the temperature is increased. Hence the manufacturing process must occur at cold temperatures. At cold temperatures there is still the possibility that the clotting proteins will be denatured by these organic solvents causing the partial or complete inactivation of the clotting proteins. A further disadvantage is that it is an economic and logistic disadvantage to have a manufacturing process which requires refrigerator temperatures. Additionally, the coagulation constitutents are dispersed throughout the collagen matrix, and may not be available at the surface of the matrix in sufficient quantities to promote coagulation.

Larson et al. (Arch Surg 1995: 130:420-422) have reported the use of a gauze dressing on which dry fibrinogen and thrombin has been placed to stop arterial bleeding in animals. The dry protein can be dislodged from the dressing, hence the dressing is not suitable as a commercial dressing. The proteins would tend to separate from the dressing during packaging and shipment, which reduces the effectiveness of the dressing.

The object of this invention is to provide a hemostatic dressing which is capable of stopping severe bleeding such as that which occurs when major blood vessels are severed.

It is another object of the invention to provide such a dressing that can be more conveniently manufactured than some prior hemostatic dressings. Yet another object is to manufacture a hemostatic dressing that more completely retains hemostatic efficacy during storage and shipment.

SUMMARY OF THE INVENTION

The present invention provides a composition for a hemostatic bandage comprising a carrier, sufficient coagulation constituents to allow blood

clot formation, wherein the constituents are in an environment such that they react only when used. The bandage includes a substance which allows the coagulation constituents to adhere to the carrier, hence when the bandage is placed on a bleeding wound and comes in contact with body fluids, the coagulation constituents react to form a clot which stops the bleeding. It is not necessary for the body fluids to contain fibrinogen, thrombin or other coagulation constituents to achieve hemostatic activity. The adhesive material that adheres the coagulation constitutents to the carrier is a viscous liquid that does not easily penetrate very deeply into the carrier, and therefore provides a higher concentration of coagulation factors on the surface of the carrier where they are needed. The viscous nature of the material also provides improved adhesiveness to the carrier.

Accordingly, the present invention provides a composition for sealing and healing wounds and which may be stored for a lengthy period while maintaining efficacy. The composition comprises a carrier which may be absorbable (so as to be able to be used internally) such as alginic acid or one of its salts, or any one of a number of other polysaccharides such as cellulose, gum xanthan, carrageenan or pectin. Gelatin, collagen or other protein capable of being formed into a carrier may also be used. Alternatively, the carrier may be non-absorbable to be used externally. Examples of non-absorbable carriers are surgical gauze, clinical felt, polyurethane foam and other material commonly used in medical practice. Said carrier is coated on one side with a viscous liquid such as propylene glycol, glycerol or a low molecular weight polyethylene glycol that is sufficiently tacky to allow the coagulation constituents to adhere to the carrier. The carrier may also be coated with water in a low concentration and/or at a low pH so as not to support reaction of the coagulation factors.

The coagulation constituents may be applied in a dried or powdered form and include 1) a thrombin component containing thrombin substances which form thrombin in the presence of body fluids, or a mixture of such substances, 2) a fibrinogen component containing fibrinogen, fibrinogen-containing Factor XIII, or a mixture of such substances. The mixture of 1 and 2 may contain additives such as calcium ions, antibiotics or other anti-infection medicaments, vasoconstrictive substances such as adrenaline, and/or growth factors.

To prepare the composition according to the invention, the carrier may be in the form of a foam, web, film or when possible, as in the case of cellulose and cotton gauze, it may be woven. Such materials are prepared in a manner well known to those skilled in the art. Additionally, an adhesive backing may be applied to the carrier.

The fibrinogen may be of human or animal origin and may be applied in the range of 0.1 to 20 mg/cm^2, preferably from 1 to 10 mg/cm^2 of surface area of the substrate. The fibrinogen may or may not contain Factor XIII. Usually fibrinogen containing 0.5 to 20 units of Factor XIII per mg of fibrinogen is employed, preferably between 2 and 10 units per mg of fibrinogen. Factor XIII may be added separately to increase its concentration if desired. The fibrinogen may be in any dry form, preferably in a powdered form to allow rapid dissolution when in contact with body fluids.

The thrombin may be of human or animal origin and may be applied in the range of 1 to 20 NIH units/mg fibrinogen, preferably 3 to 12 NIH units/mg fibrinogen. In place of thrombin, any substance or substances that liberate thrombin may replace thrombin. Examples of such factors include Factor X or Xa plus prothrombin, any of the various enzymes from snake venom that liberate thrombin from prothrombin such as that from the viper Echis carinatus plus prothrombin, or enzymes which convert fibrinogen to fibrin such as that from the viper Bothrops atrox plus prothrombin.

In addition to the coagulation factors, other substances such as growth factors to promote healing, calcium ions to aid coagulation and Factor XIII activity, adrenaline or other substances to constrict blood vessels to aid in hemostasis and bactericides to prevent infection.

In order for the coagulation factors and other substances to adhere to the carrier, the carrier is coated on one or both sides with a sticky biocompatible non-aqueous substance, that does not denature the coagulation factors nor participate in or activate the enzymatic clotting reaction involving the coagulation factors. Such substances include but are not limited to carbohydrates, such as saccharides, for example monosaccharides (such as glucose), oligosaccharides (such as maltose), polysaccharides (such as glycogen). The sticky, biocompatible substances could also be a polyhydric alcohol such as glycerol or other organic

adhesive polymers, such as polyethylene glycol having a molecular weight of about 200 to 400 daltons, and propylene glycol. In another embodiment the carrier may be lyophilized in the presence of the viscous liquid. Alternatively, the carrier may be coated with a very small amount of water preferably at a pH of about 4 to 6 to allow the substances to stick but not to react.

The dry powdered coagulation factors and other substances may be mixed together and added at once or they may be added sequentially. The solids are preferably milled to a fine powder to enhance their solubility and when added together it is preferable to mix them thoroughly in a blender before binding them to the carrier.

DETAILED DESCRIPTION OF SOME PREFERRED EMBODIMENTS

In a preferred embodiment, the composition is a solid, fibrous matrix, such as cotton gauze or alginic acid, suitable for placement as a pad applied over or inserted into an open bleeding wound. A mixture of intermingled particles of powdered coagulation factors, preferably fibrinogen and thrombin, are present alongside one another in the matrix to readily interact when moistened by blood or other aqueous body fluids that provide an aqueous liquid reaction medium. The particles are adhered to the sold matrix by a viscous nonaqueous adhesive material, such as a viscous polysaccharide, polyethylene glycol, or petroleum jelly, that interferes with or does not participate in the enzymatic clotting reaction involving the coagulation factors at room temperature and at physiologic pH (about 7.3-7.4).

The thrombin/fibrinogen reaction is hydrolytic and requires an aqueous medium for the fibrin clot to be formed. The viscous adhesive is substantially free of water, and therefore substantially prevents fibrin clot formation. The nonaqueous viscous adhesive preferably contains less than 15% by weight water, preferably less than 10%, most preferably less than 3% water. Weights are expressed in weight percent of the final product (which includes matrix, viscous adhesive, and coagulation factors).

In the preferred embodiment, the polysaccharide or other adhesive material is sufficiently tacky to adhere to the matrix a sufficient amount of the commingled particles of the powdered coagulation factors to form a clot when the matrix is exposed to an aqueous solution, blood from a wound, or body

fluids, such as serosanguinous fluid or cerebrospinal fluid. The clot that is formed is sufficient to reduce or stop bleeding or leaking from a wound, such as an abrasion, spinal needle puncture, laceration, avulsion or surgical incision.

The invention also includes clotting compositions made by the method of adhering particles of the powdered coagulation factors to the matrix, such as a cotton gauze or an alginic acid matrix. The particles are adhered to the matrix by the viscous adhesive material, which maintains the physically commingled particles within the matrix, near the surface, but inhibits clotting action until the matrix is exposed to an aqueous medium that dissolves the particles and permits participation of the coagulation factors in the clotting cascade, and formation of a fibrin clot.

The method by which the composition is made includes applying the viscous adhesive to the matrix, followed by application of a mixture of solid thrombin and fibrinogen particles to the matrix. Alternatively, the thrombin and fibrinogen particles can be suspended in the nonaqueous viscous adhesive liquid that inhibits or prevents the hydrolytic reaction and fibrin clot formation. This viscous mixture containing the particles can be applied as a slurry directly to the surface or surfaces of the matrix. The high viscosity of the adhesive inhibits absorption of the adhesive and suspended particles deep into the matrix, such that the particles remain relatively available for participation in clotting reactions during use. The composition can be prepared at and stored without refrigeration. Preparation and storage can occur, for example, at 20-35°.

Methods of use of the composition include applying the composition to the surface of an abrasion, laceration, puncture, avulsion, surgical incision or other injury to promote clotting and stop bleeding. The composition can also be packed into open wounds by physicians or emergency medical personnel, to promote coagulation and diminish blood loss. The composition is particularly useful at stopping life-threatening arterial blood loss that can lead to exsanguination. It is preferred to apply one of the coated surfaces of the composition directly to the source of bleeding, such as an abraded dermal surface.

The invention is further explained by the following examples, which, however do not constitute a limitation thereof.

EXAMPLE 1

A 2% solution of low viscosity sodium alginate from Macrocystis pyrifira (Sigma Chemical Co., St. Louis, MO) was prepared by dissolving the alginate in water at 60°. Ten mL of this solution was placed in a round aluminum mold 4.4 cm in diameter (15 cm^2), frozen at -20° and lyophilized. The lyophilization was carried out with the product at room temperature, the condenser at -40° to -50° and the vacuum at 30 to 60 millitorr. The resulting pad was dipped at room temperature into a suspension of 100 mg bovine fibrinogen (56% protein, 95% clottable, Sigma Chemical Co., St. Louis, MO) and 6 mg bovine thrombin [56 NIH units/mg (as determined by direct comparison to NIH thrombin reference standard J), Sigma Chemical Co., St. Louis, MO] in 3 mL polyethylene glycol (average molecular weight 300, viscosity 5.8 centistokes or 6.5 centipoise at 210°F, Sigma Chemical Co., St. Louis, MO) so as to coat the pad at room temperature (about 25°C) with the fibrinogen thrombin mixture. The pad was kept at room temperature for 15 to 30 minutes to ensure that no clot would form. Then, in order to test the ability of the resulting pad to form a clot when exposed to an aqueous environment the pad was placed in a small dish (4.4 cm diameter) containing 4 mL of 40 mM Tris, pH 7.4 and 5 mM $CaCl_2$ at 37°. In less than 30 seconds, a clot formed which adhered tightly to the bottom of the dish.

The test described in this and other examples can be used as an assay to select other adhesive materials, reactant amounts, reaction conditions, and other process parameters that will produce a product that forms a clot when exposed to body fluids under conditions of use.

EXAMPLE 2

A pad of sodium alginate prepared as in Example 1, was dipped in a 4.4 cm diameter aluminum dish containing 100 mg of bovine fibrinogen, 5 mg of bovine thrombin (the same proteins that were described in Example 1) in 3 mL of glycerol (viscosity of 1497 cps at 20°C, Sigma Chemical Co., St. Louis, MO). After standing for 15 to 30 minutes the pad was dipped in an aluminum dish (4.4 cm diameter) containing 2 mL of 40 mM Tris pH 7.4 and 5 mM $CaCl_2$ at 37°. In less than 30 seconds, a clot formed which adhered tightly to the bottom of the dish.

EXAMPLE 3

Nine mL of a sodium alginate solution prepared as in Example 1 was mixed with 1 mL of polyethylene glycol of average molecular weight 300 and placed in a 4.4 cm diameter aluminum dish and lyophilized as in Example 1. Similarly, 8.5 mL of this solution was mixed with 1.5 mL of polyethylene glycol, average molecular weight 400 (viscosity 7.3 centistokes or 8.2 centipoise at 210°F, Sigma Chemical Co., St. Louis, MO) and 8 mL was mixed with 2 mL of polyethylene glycol average molecular weight 400 or 2 mL of polyethylene glycol average molecular weight 400 or 2 mL of polyethylene glycol average molecular weight 300 and lyophilized as above. The pads produced this way were more flexible than those made without polyethylene glycol and the flexibility and tackiness increased with increasing amounts of polyethylene glycol. There were no noticeable difference between the 300 and 400 molecular weight polyethylene glycol.

EXAMPLE 4

To 13 mL of a 2% sodium alginate solution prepared as in Example 1, add 2 mL of 1M $CaCl_2$. Place in 4.4 cm diameter aluminum mold and lyophilize as in Example 1. This produced a pad of sodium-calcium alginate which was more rigid than the sodium alginate alone.

EXAMPLE 5

A 2% solution of carrageenan (vegetable gelatin from Irish Moss, Type 1, Sigma Chemical Co., St. Louis, MO) was prepared by dissolving the carrageenan in water at 60° to 80°. Ten mL of this solution was placed in a round aluminum mold 4.4 cm in diameter (15 cm^2), frozen at -20° and lyophilized. Eight mL of this solution was mixed with 2 mL of polyethylene glycol average molecular weight 400 and placed in a round aluminum mold 4.4 cm in diameter and lyophilized. The lyophilization was carried out with the product at room temperature, the condenser at -40° to -50° and the vacuum at 30 to 60 millitorr. The pad without the polyethylene glycol was brittle while the one with polyethylene glycol was very soft, pliable and tacky. The pad that was prepared with polyethylene glycol was placed in a small dish containing 100 mg bovine fibrinogen (56% protein, 95% clottable, Signa Chemical Co., St. Louis, MO) and 7 mg bovine thrombin [56 NIH units/mg (as determined by direct

comparison to NIH thrombin reference standard J) bovine thrombin, Sigma Chemical Co., St. Louis, MO]. The pad was pressed firmly into the dry powder so as to impregnate the powder into the pad. The pad was kept at room temperature for one hour to ensure that no clot would form. Then, in order to test the ability of the resulting pad to form a clot when exposed to an aqueous environment the pad was placed in a small dish (4.4 cm diameter) containing 3 mL of 40 mM Tris, pH 7.4 and 5 mM $CaCl_2$ at 37°. In 30 to 40 seconds, a clot formed which adhered tightly to the bottom of the dish.

EXAMPLE 6

A 2% solution of gum xanthan (Practical Grade, Sigma Chemical Co., St. Louis, MO) was prepared by dissolving the gum in water at 60° to 80°. Ten mL of this solution was placed in a round aluminum mold 4.4 cm in diameter (15 cm^2). Eight mL of this solution was mixed with 2 mL of polyethylene glycol average molecular weight 400 and placed in a round aluminum mold 4.4 cm in diameter. Both molds were frozen at -20° and lyophilized as in Example 5. The pad without the polyethylene glycol was brittle while the one with polyethylene glycol was very soft, pliable and tacky.

EXAMPLE 7

A gauze bandage was folded into a three layer square of 36 cm^2. Two mL of polyethylene glycol, molecular weight 400 daltons, was spread evenly over the gauze. A mixture of 100 mg of fibrinogen and 4 mg of thrombin were applied to the gauze. Four mL of Tris buffer, pH 7.4 and 5 mM $CaCl_2$ was placed in a plastic dish so as to form a shallow layer. The solution was heated to 37° and the thrombin and fibrinogen containing gauze was placed in the dish. In less than one minute, the gauze was firmly attached to the bottom of the dish by the fibrin clot which formed.

EXAMPLE 8

A carrageenan pad prepared without polyethylene glycol as in Example 5 was coated with a thin film of petroleum jelly. Then 100 mg bovine fibrinogen (56% protein, 95% clottable, Sigma Chemical Co., St. Louis, MO) and 7 mg bovine thrombin [56 NIH units/mg (as determined by direct comparison to NIH thrombin reference standard J), Sigma Chemical Co., St. Louis, MO] was impregnated into the pad. The pad was kept at room

temperature for one hour to ensure that no clot would form. To test the ability of the resulting pad to form a clot when exposed to an aqueous environment, the pad was placed in a small dish (4.4 cm diameter) containing 3 mL of 40 mM Tris pH 7.4 and 5 mM $CaCl_2$ at 37°. In 30 to 40 seconds, a clot formed which adhered tightly to the bottom of the dish.

EXAMPLE 9

A 4% solution of low viscosity sodium alginate from Macrocystis pyrifira (Sigma Chemical Co., St. Louis, MO) was prepared by dissolving the alginate in water at 60°. Fifteen mL of this solution was placed in a round aluminum mold 4.4 cm in diameter (15cm^2, frozen at -20°) and lyophilized. The lyophilization was carried out with the product at room temperature, the condenser at -40° to -50° and the vacuum at 30 to 50 millitorr. The resulting cake was 10 mm thick. The cake was attached to a Bertek Inc. (St. Albans VT) medical laminate consisting of copolyester film 325, PSA adhesive 737 and release liner 2114. The adhesive allowed the pad to adhere firmly to the film. The resulting pad was dipped at room temperature into a suspension of 200 mg bovine fibrinogen (56% protein, 95% clottable, Sigma Chemical Co, St. Louis, MO) and 10 mg bovine thrombin [56 NIH units/mg (as determined by direct comparison to NIH thrombin reference standard J, Sigma Chemical Co., St. Louis MO] in 3 mL polyethylene glycol (average molecular weight 300, viscosity 5.8 centistokes at 210°F, Sigma Chemical Co., St. Louis, MO) so as to coat the pad with the fibrinogen/thrombin mixture. The pad was kept at room temperature for two hours to ensure that no clot would form. Then, in order to test the ability of the resulting pad to form a clot when exposed to an aqueous environment, the pad was placed in a small dish (44 x 12.5 mm) containing 4 mL of 40 mM Tris, pH 7.4 and 5 mM $CaCl_2$ at 37°C. Pressure was applied to the pad by taping the ends of the film firmly to the tabletop. After two minutes, the tape was peeled from the tabletop and was easily separated from the pad. The pad strongly adhered to the dish due to the fibrin clot.

For external use this type of hemostatic dressing can be applied with pressure by adhering the film to the skin adjacent to the wound. As the film is permeable to air but not to liquids, it can be left in place until healing occurs or the film can be replaced when necessary. For an internal dressing for large

openings, the film could be applied with pressure and secured in place with surgical staples. After the clot has set, the staples would be removed and the film peeled from the pad leaving the clot and the absorbable pad in place. For a completely absorbable dressing the pad could be attached to an absorbable mesh (made of polyglycolic acid for example) instead of the copolyester film.

As used in this specification, the term "viscous" means having a viscosity higher than 100 centipoise at 20°C. In many embodiments of the invention, the viscous liquid has a viscosity of at least 1000 centipoise, for example 1×10^3 to 1×10^{16} centipoise at 20°C. Examples of the viscosities (in centipoise) of some of the disclosed adhesive materials at 20°C include: sucrose at 2.8×10^6, glycerol at 1,490, and glucose at 9.1×10^{15}. These very high viscosities contrast with the relatively low viscosities of solvents (in centipoise) such as n-butyl alcohol (2.9 at 20°C), propanol (1.30 at 50°C), isobutanolol (4.7 at 15°C) and acetone (0.316 at 25°C).

A "nonaqueous liquid" is one that has less than 15% water by weight, although some embodiments of the nonaqueous liquid have less than 3% water by weight, for example 1-3% water by weight.

"Body fluids that activate clotting" include liquid blood (including whole blood or plasma), serosanguinous fluid, cerebrospinal fluid, and other fluids produced by the human body that provide a continuous medium that is sufficiently aqueous, and at a physiological pH, that initiates the clotting cascade.

A "saccharide" is a sugar, which is a type of carbohydrate. Examples include maltose, glucose, ethyrose, arabinose and fructose. A monosaccharide (such as glucose) is a saccharide that is not hydrolyzable into smaller units. A disaccharide (such as maltose) yields two equivalents of the monosaccharide upon hydrolysis under mildly acidic conditions. An oligosaccharide is a saccharide polymer continuing up to eight saccharide subunits. A polysaccharide is a polymer in which the number of subunits is greater than eight, for example 100-300 subunits.

Propylene glycol refers to 1,2-propaneglycol. Glycerol is 1,2,3-propanetriol. Petroleum jelly is also known as petrolatum (U.S.P.) or mineral jelly. Polyethylene glycol is a condensation polymer of ethylene glycol, having average molecular weights ranging from about 200 to 6000.

Having illustrated and described the principles of the invention in several embodiments, it should be apparent to those skilled in the art that the invention can be modified in arrangement and detail without departing from such principles. I claim all modifications coming within the spirit and scope of the following claims.

I claim:

1. A composition for decreasing a flow of blood from a wound, comprising:

a carrier;

coagulation constituents adhered to the carrier by an adhesive selected from the group consisting of water at a pH at which thrombin and fibrinogen do not interact to form fibrin, and a viscous nonaqueous biocompatible adhesive, the coagulation constituents being present in a therapeutically sufficient amount to clot and decrease the flow of blood from the wound when the composition contacts body fluids that activate clotting.

2. The composition of claim 1, wherein the adhesive is a nonaqueous liquid at 20°C, and the adhesive adheres the coagulation constituents to the carrier.

3. The composition of claim 2, wherein the carrier is biologically absorbable.

4. The composition of claim 2, wherein the nonaqueous adhesive is selected from the group consisting of propylene glycol, glycerol, petroleum jelly and polyethylene glycol.

5. The composition of claim 2, wherein the coagulation constituents are selected from the group consisting of thrombin, fibrinogen, biological precursors of thrombin, biological precursors of fibrin, and mixtures thereof.

6. The composition of claim 5 wherein the coagulation constituents comprise fibrinogen present in an amount of 0.1 to 20 mg/cm^2, and thrombin present in an amount of 1 to 20 NIH units/mg fibrinogen.

7. The composition of claim 6, further comprising Factor XIII.

8. The composition of claim 1, wherein the adhesive is water at a pH of about 4-6.

9. The composition of claim 1, wherein the coagulation constituents are intermingled next to one another on a surface of the carrier, and adhered to the carrier by the adhesive, without being dispersed throughout the carrier.

10. A hemostatic wound dressing, comprising:

a fibrous matrix suitable for placement as a pad applied over or inserted into an open, bleeding wound;

a mixture of intermingled particles of powdered coagulation factors present on the surface of the matrix, the particles being in sufficiently close contact with each other to form a clot when exposed to an aqueous medium at a physiological pH, the particles being adhered to the matrix by a viscous nonaqueous adhesive, having a viscosity of at least 100 centipoise at 20°C, that inhibits a clotting reaction between the intermingled particles until the particles are exposed to an aqueous medium at physiological pH.

11. The wound dressing of claim 10, wherein the adhesive is selected from the group consisting of a polysaccharide, polyethylene glycol, propylene glycol, glycerol, and petroleum jelly.

12. The wound dressing of claim 10, wherein the adhesive is applied to the matrix in a liquid form comprising less than 15% by weight water.

13. The wound dressing of claim 12, wherein the adhesive is applied to the matrix in a liquid form comprising less than 3% by weight water.

14. The wound dressing of claim 13, wherein the matrix is selected from the group consisting of cotton gauze and an alginic acid matrix.

15. A hemostatic wound dressing, comprising:

a fibrous matrix suitable for placement as a pad applied over or inserted into an open, bleeding wound;

a mixture of intermingled particles of powdered coagulation factors present throughout the matrix, in sufficiently close contact to form a clot when exposed to an aqueous medium at a physiological pH, the particles being adhered to the matrix by a viscous nonaqueous adhesive that inhibits a clotting reaction between the intermingled particles until the particles are exposed to an aqueous medium at physiological pH, wherein the adhesive is selected from the group consisting of a polysaccharide, polyethylene glycol, propylene glycol, glycerol, and petroleum jelly, which adhesive has been applied to the matrix in a liquid form comprising less than 3% by weight water.

16. The hemostatic wound dressing of claim 15, wherein the coagulation factors are fibrinogen present in an amount of 0.1 to 20 mg/cm^2, and thrombin present in an amount of 1 to 20 NIH units/mg fibrinogen

17. A method of making a hemostatic wound dressing, comprising the steps of:

providing a fibrous matrix;

dispersing and adhering an intermingled mixture of coagulation constituents throughout the matrix in a therapeutically sufficient amount to clot blood flowing from the wound when the coagulation factors contact body fluids that activate clotting, by applying fibrinogen and thrombin, or precursors thereof, to the matrix with a viscous, nonaqueous adhesive.

18. The method of claim 17, wherein the viscous adhesive is selected from the group consisting of a polysaccharide, polyethylene glycol, propylene glycol, glycerol, and petroleum jelly.

19. The method of claim 17, wherein the viscous adhesive is applied to the matrix, and the coagulation constituents are then applied to the matrix.

20. The method of claim 17, wherein the adhesive is applied to the matrix at a temperature of at least 20°C.

21. A method of clotting blood flowing from a wound, comprising the step of applying the composition of claim 1 to a bleeding wound for a sufficient period of time to clot blood flowing from the wound.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/01901

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61L 15/00; A61K 9/70, 35/14, 38/00; A01N 1/02
US CL :424/177.1, 402, 405; 604/368; 427/2
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/177.1, 402, 405; 604/368; 427/2

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,453,939 A (ZIMMERMAN ET AL.) 12 June 1984, column 1, line 54 - column 3, line 68.	1-21
Y	US 4,683,142 (ZIMMERMAN ET AL.) 28 July 1987, column 3, line 12 - column 6, line 46.	1-21
Y	US 4,600,574 A (LINDNER ET AL.) 15 July 1986, column 1, line 48 - column 2, line 4.	1-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 05 MAY 1997	Date of mailing of the international search report 22 MAY 1997
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer KATHRYNE SHELBORNE